







# A Retrospective Study on the Clinical, Laboratory, and Nutritional Status of Pediatric Epidermolysis Bullosa in a Tertiary Referral Hospital in West Java, Indonesia

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**Background:** Epidermolysis bullosa (EB) is a genodermatosis disease with bullae and erosions of the skin and mucous membrane that can last for a lifetime and decrease quality of life. Oral and gastrointestinal disorders inhibit the patients' ability to achieve optimal nutrition, making the patients prone to infection, leading to prolonged wound healing, and delayed growth and developmental process. However, there has been no research on the clinical, laboratory, and nutritional status of pediatric EB patients in Indonesia.

**Purpose:** This study aims to describe the clinical, laboratory, and nutritional characteristics of pediatric EB patients treated in Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

**Patients and Methods:** This was a retrospective descriptive study of pediatric EB patient records in Dermatology and Venereology Outpatient of Dr. Hasan Sadikin General Hospital Bandung, Indonesia, from April 2018-March 2020.

**Results:** Study results showed 12 pediatric EB patients consisting of 7 dystrophic EB (DEB) (4 recessive dystrophic EB [RDEB] patients and 3 dominant dystrophic EB [DDEB]), 3 junctional EB (JEB), and 2 EB simplex (EBS). The most extensive EB wounds was found affecting 10–20% of the body surface area with a <10% infected wound area. Pain was found in all patients. The most frequent abnormalities in laboratory examination were anemia and low zinc levels. Severe malnutrition was found in almost half of the patients.

**Conclusion:** RDEB is the most commonly found type of pediatric EB. Wounds on the skin, tooth decay, hand deformity, pain when changing dressings, low zinc levels, and low hemoglobin levels are the clinical features and laboratory findings that contribute to the development of moderate and severe malnutrition in RDEB patients.

**Keywords:** clinical, epidermolysis bullosa, laboratory, nutritional status

## Introduction

Epidermolysis bullosa (EB) is a rare autosomal genodermatosis disease characterized by the formation of bullae and erosions of the skin and mucous membranes,<sup>1</sup> indicating that the skin and mucosa are brittle<sup>2</sup> and vulnerable to spontaneous mechanical trauma<sup>3</sup> or friction.<sup>1</sup> Mutations of the gene encoding the basement membrane zone (BMZ) protein are linked to its etiopathogenesis.<sup>3</sup> According to the 2014 Consensus, there are four primary types of EB: simplex EB (EBS), junctional EB (JEB), dystrophic EB (DEB) (either recessive dystrophic EB [RDEB] and dominant dystrophic EB [DDEB]), and Kindler syndrome (KS).<sup>1,3,4</sup> Bullae, erosions, and crusts exist in all kinds of EB.<sup>3</sup> Additionally, milia, nail dystrophy, and anonychia may also develop in EB.<sup>5</sup> Extracutaneous involvement occurs in numerous subtypes of

EB, particularly in the generalized and severe subtypes. Oropharynx, trachea, esophagus, eyes, hair, and teeth are commonly affected.<sup>1,6</sup>

The main complications of the chronic erosive lesions of EB are secondary bacterial infection<sup>7</sup> and squamous cell carcinoma.<sup>2</sup> Chronic wounds in EB patients may lead to anemia, nutritional disorder, and limited physical activity, which will decrease the patient's quality of life, resulting in failure to thrive, and death.<sup>8</sup> To date, there has been no causative treatment for EB.<sup>2</sup> Management of wound healing in addition to preventing new lesions and supportive therapy are priorities in the treatment of EB patients.<sup>9</sup> Nutritional balance is required in chronic wounds, as it contributes to wound healing and the prevention of secondary bacterial infections.<sup>7</sup> Optimal hemoglobin, ferritin, zinc, and albumin levels are factors for optimal wound healing.<sup>10–12</sup>

There have been no clinical, laboratory, or nutritional studies of pediatric epidermolysis bullosa patients in Indonesia. Therefore, the authors are interested in studying the clinical, laboratory, and nutritional characteristics of EB patients treated at Dr. Hasan Sadikin General Hospital Bandung. The findings of this study are expected to provide scientific information on the clinical outcomes, laboratory findings, and nutritional status of pediatric EB patients at Dr. Hasan Sadikin General Hospital Bandung. Furthermore, the findings of this study are expected to be used as a model for future research and management of pediatric EB patients.

## Materials and Methods

This study was conducted at Dr. Hasan Sadikin Hospital Bandung, an Indonesian Tertiary Referral Hospital located in the West Java province, and has been approved by the Institutional Review Board of Health Research Ethics Committee at Dr. Hasan Sadikin Hospital. Parents/legal guardians of every study participant gave consent before study commencement. In this retrospective study, hospital patient records from April 2018 to March 2020 were analyzed. These registers were maintained in the outpatient department of the Pediatric Dermatology Clinic at Dr. Hasan Sadikin General Hospital Bandung and contained information regarding patients' history, physical examination, body weight, height, and blood examination.

Ethical clearance was obtained from the ethical committee of the institute. Total sampling technique was used; thus, all medical records that fulfilled the inclusion criteria were included in the study. Inclusion criteria were medical records of newly-admitted pediatric EB patients as diagnosed by a dermatologist based on clinical findings from April 2018 – March 2020 that include the patients' history, physical examination, body weight, height, and blood examination. Exclusion criteria were medical records that were damaged or indecipherable and medical records that were unavailable. Data were then entered into Microsoft Excel for statistical analysis.

Variables in this study were clinical features, laboratory results, and nutritional status. The clinical features studied were onset of illness, duration of illness, type of EB, and clinical factors affecting nutritional status. The latter refer to skin involvement (percentage of EB wound area and percentage of infected EB wound area based on body surface area [BSA], according to the EB Clinical Practice Guidelines); gastrointestinal involvement (oral blisters or sores, microstomia, ankyloglossia, tooth decay, dysphagia, odynophagia, heartburn, epigastric pain, constipation, painful defecation); extraintestinal involvement (hand deformity [pseudosyndactyly] and pain when changing dressings). Laboratory parameters affecting wound healing included hemoglobin, ferritin, albumin, and zinc levels. Nutritional status was assessed using a weight for height chart for children aged <5 years old and a body mass index for age chart for children >5 years old based on World Health Organization (WHO) Z-scores growth charts.

## Results

A total of 12 medical records of EB patients were assessed, consisting of records of 6 girl and 6 boy patients. Based on the age group, there were 6 patients aged 1–5 years (the largest age group in this study), 4 patients aged <1 year, and 2 patients aged 11–15 years old. The youngest EB patient was 9 days old and the oldest was 15 years old with a mean of  $3.8 \pm 4.7$  years old. In terms of patients' recent education, the majority of patients did not go to school due to the fact that 10 patients were not yet of school age and 1 patient decided not to go to school. Only one patient went to school and graduated from elementary school.

The most common type of EB in this study was DEB with 7 patients (4 RDEB and 3 DDEB), followed by JEB (n = 3), and EBS (n = 2). The onset of illness in all patients occurred before 1 year old, as the first complaint was felt since birth or shortly after birth. The clinical features of 12 pediatric EB patients showed that erosion was the most frequent skin involvement as it was found in all patients. Other skin involvements, such as bullae was found in 10 patients, scars in 8 patients, vesicles in 7 patients, and milia in 5 patients. Nail abnormalities were more commonly found on toenails (11 patients) compared to fingernails (7 patients). Oral and throat mucosal abnormalities were seen in 5 patients.

Skin, gastrointestinal, and extraintestinal involvement as clinical factors influencing nutritional status were studied and are shown in Table 1. Most patients had wound areas in the range of 10–20% BSA, mostly found in JEB and DEB patients, and infected wound areas were <10% BSA, commonly found in DEB patients. Twenty gastrointestinal symptoms were recorded as each patient showed more than 1 gastrointestinal involvement. These symptoms were mostly found in DEB patients. Extraintestinal involvement was mostly in the form of pain, especially when changing wound dressings. This was found in all types of pediatric EB patients.

Table 2 shows the laboratory examination and nutritional status of pediatric EB patients. Hemoglobin level was measured in all patients as part of routine blood work-up. The number of patients with low hemoglobin levels was proportional to those with normal hemoglobin levels. Most patients who had their ferritin level and albumin level

**Table 1** Clinical Factors Affecting Nutritional Status

Variable	EBS	JEB	DEB		Total (n)
			RDEB	DDEB	
<b>Skin involvement (n=12)</b>					
<b>Percentage of EB wound area (BSA)</b>					
<10%	0	0	1	0	1
10–20%	2	3	1	2	8
>20%	0	0	2	1	3
<b>Percentage of infected EB wound area (BSA)</b>					
No infection	0	1	2	1	4
<10%	2	2	2	2	8
10–20%	0	0	0	0	0
>20%	0	0	0	0	0
<b>Gastrointestinal involvement (n=12)</b>					
Oral blisters or sores	0	1	3	1	5
Microstomia	0	0	1	0	1
Ankyloglossia	0	0	1	0	1
Tooth decay*	1	1	2	2	6
Disphagia	0	0	0	0	0
Odinophagia	0	1	3	1	5
Heartburn	0	0	0	0	0
Epigastric pain	0	0	0	0	0
Constipation	0	0	1	0	1
Painful defecation	0	0	1	0	1
<b>Extraintestinal involvement (n=12)</b>					
Hand deformity					
Yes	0	0	1	0	1
No	2	3	3	3	11
Pain when changing dressing					
Yes	2	3	4	3	12
No	0	0	0	0	0

**Note:** \*Only assessed in patients who have had teeth eruption.

**Abbreviations:** BSA, body surface area; EB, epidermolysis bullosa; n, noun.

**Table 2** Laboratory and Nutritional Status in Pediatric EB Patients

Patient ID	Diagnosis	Age	Laboratory Examination								Nutritional Status	
			Hemoglobin		Ferritin		Albumin		Zinc		Z-scores	Category
			Level (g/dl)	Category	Level (ng/mL)	Category	Level (g/dl)	Category	Level (µg/dl)	Category		
1	JEB	9 days	13	Normal	N/A	N/A	N/A	N/A	56	Low	<-1 SD >-2	Normal
2	JEB	11 months	9,7	Anemia	82,8	Normal	2,9	Hypoalbuminemia	N/A	N/A	<-3 SD	Severe malnutrition
3	EBS	1 years	12,6	Normal	23	Normal	4,3	Normal	76	Normal	<-2 SD >-3	Moderate malnutrition
4	DDEB	2 years	12,4	Normal	N/A	N/A	4,5	Normal	80	Normal	2 SD	At risk of obese
5	EBS	4 years	13,3	Normal	42	Normal	3,6	Normal	39	Low	<-2 SD >-3	Moderate malnutrition
6	RDEB	5 years	14,3	Normal	37	Normal	4,1	Normal	59	Low	<2 SD >1	At risk of obese
7	DDEB	15 years	7,8	Anemia	2	Low	3,9	Normal	72	Normal	<-3 SD	Severe malnutrition
8	DDEB	5 months	12,7	Normal	33	Normal	4,1	Normal	121	Normal	2 SD	At risk of obese
9	RDEB	4 years	9,2	Anemia	5	Low	2,9	Hypoalbuminemia	57	Low	<-3 SD	Severe malnutrition
10	RDEB	11 years	9,7	Anemia	N/A	N/A	2,4	Hypoalbuminemia	60	Low	<2 SD >1	Overweight
11	JEB	28 days	9,5	Anemia	1337,8	Normal	1,63	Hypoalbuminemia	N/A	N/A	<-3 SD	Severe malnutrition
12	RDEB	1 years	11	Anemia	11	Low	4,1	Normal	59	Low	<-2 SD >-3	Moderate malnutrition

**Abbreviations:** DEB, Dystrophic EB; DDEB, Dominant DEB; EBS, EB Simplex; JEB, Junctional EB; N/A, not available, not examined; RDEB, Recessive DEB; SD, standard deviation.

measured had normal levels for both parameters. In contrast, low zinc level was mostly found in patients who had their zinc level measured. In terms of nutritional status, only 1 patient was observed to have normal nutritional status while the other 11 patients had abnormalities, including 4 patients (2 JEB and 2 DEB patients) with severe malnutrition, 3 patients (2 EBS and 1 DEB patient) with moderate malnutrition, 3 DEB patients at risk of obesity, and 1 DEB patient was overweight.

## Discussion

According to the literature, the most common type of EB is EBS.<sup>1</sup> This study found that the most common type of EB in a Tertiary Referral Hospital in West Java, Indonesia, was RDEB, followed by DDEB, JEB, and EBS. Morales-Olvera et al<sup>13</sup> found that RDEB followed by DDEB was the common type of EB at The National Institute of Pediatrics, Mexico. Danescu et al<sup>4</sup> also found that the most common type of EB was DEB which occurred in as many as 58 of 89 subjects. DEB was found to be the most common type of EB in previous studies due to the fact that other EB patients were not diagnosed by dermatologists due to limitations in the data registry.<sup>4</sup> The result shown in this study is presumably because DEB patients who seek treatment were already in severe condition. In addition, low socioeconomic status, low awareness of medical care, and low education of EB in Indonesia might lead to undiagnosed EB, and therefore accurate data cannot be obtained.

Clinical factors influencing nutritional status were skin,<sup>9</sup> gastrointestinal, and extraintestinal involvement.<sup>2</sup> Wound assessment of EB can be done based on the body surface area or affected BSA.<sup>9</sup> The largest EB wound lesion area was 10–20%, found in 8 patients. The largest percentage of infected EB wound lesions was <10%, found in 8 patients. This is in accordance with the study by Zidorio et al<sup>14</sup> who reported in their study that the largest EB wound lesion area was <10% in 8 patients. Skin involvement and infected skin in pediatric EB patients were spontaneous or caused by friction or trauma.<sup>3</sup> Persistent friction and trauma might lead to secondary infections.<sup>1</sup>

The most frequent gastrointestinal manifestations found in this study were tooth decay, odynophagia, and oral blisters. Tooth decay was observed in 6 patients with RDEB and JEB. This condition may cause difficulty in chewing, resulting in decreased nutritional intake and calories, as well as decreased nutritional status in EB patients.<sup>2</sup> Oral blisters and odynophagia were found in 5 patients. The buccal mucosa, tongue, palate, and pharynx are the most frequently affected mucosa in RDEB.<sup>15</sup> The presence of bullae and erosions in the oral cavity may cause pain when eating and drinking,<sup>16</sup> while complaints of acute dysphagia<sup>16</sup> were not found in patients with bullae and erosions on the oral mucosa. These may cause inadequate intake and further affect nutritional status in EB patients.<sup>2</sup>

Hand deformity was found in 1 patient as an extraintestinal involvement in this study. The deformity is caused by repeated hand injuries leaving progressive scarring tissue which can become quite extensive. Pseudosyndactyly is a hand deformity in EB patients that results from a closure of the digits in a “mitten” of skin. EB patients who have progressive scarring of the hand may develop flexion contracture<sup>14</sup> which disturbs eating, resulting in decreased food intake.<sup>2</sup> This study found that all EB patients felt pain, especially when changing dressings. Poor nutritional status in EB patients can affect the severity of pain.<sup>2</sup>

The most common laboratory abnormalities in this study were anemia and low zinc levels. In this study, half of the pediatric EB patients were anemic. The incidence of anemia in this study is consistent with a previous study,<sup>17</sup> which reported that anemia was more common in JEB and RDEB. The cause of anemia in pediatric EB patients is thought to be due to the chronicity of the disease<sup>17</sup> that appears in 2 of 6 EB patients with anemia who have had EB for 11–15 years. In addition, anemia in this study may be caused by extensive skin lesions that may cause chronic bleeding. Decreased intake of high-iron foods, such as meat, liver, and green vegetables (spinach, kale, and broccoli) might also be contributory.<sup>2</sup> Six out of 10 pediatric EB patients were found to have low zinc levels (1 EBS patient, 1 JEB patient, and 4 RDEB patients). The presence of zinc deficiency may lead to impaired wound healing due to decreased activation of nuclear factor (NF)- $\kappa$ B, proinflammatory cytokines such as IL1 $\beta$ , tumor necrosis factor (TNF)- $\alpha$ , and neutrophil infiltration during the early wound healing process.<sup>18</sup> The cause of the decreased zinc levels in pediatric EB patients in this study is thought to be due to a decrease in the intake of foods high in zinc, such as breast milk in patients who were still breastfeeding, as well as meat, fish, and shellfish in patients who had received solid food.<sup>19</sup> These might be caused by a disturbance in eating due to mouth blisters and odynophagia.

The WHO recommends using the Z-scores threshold system that can be found on growth charts to assess nutritional status.<sup>20</sup> In this study, severe malnutrition was found in 4 patients (2 JEB, 1 RDEB patient, and 1 DDEB patient) while moderate malnutrition was observed in 3 patients (2 EBS and 1 DEB patient). This is in line with a study conducted by Morales-Olvera et al<sup>13</sup> who reported that the frequency of malnutrition was high in EB patients (82.3%). Their study found that RDEB and JEB patients frequently had chronic malnutrition, wasting, and stunting. A study by Birge<sup>21</sup> also found that 27 out of 35 DEB patients (77%), 4 of 7 JEB patients (57%), and 4 out of 18 EBS patients (22%) had a risk of malnutrition. Nutritional balance in EB patients is one of the components of comprehensive management in pediatric EB patients.<sup>22</sup> Assessment of nutritional status and early nutritional interventions affect nutritional intake in pediatric EB patients.<sup>23</sup> In addition, optimal nutrition can improve nutritional status,<sup>21</sup> reduce morbidity and mortality,<sup>23</sup> increase growth and development,<sup>24</sup> improve clinical manifestations,<sup>25</sup> promote healing, decrease susceptibility to infection, and improve the quality of life of pediatric EB patients.<sup>23</sup>

This study was not without its limitations. One limitation lies in the fact that the medical records of pediatric EB patients were not completed thoroughly and in detail, resulting in missing or unavailable data. Medical records of EB patients should be completed, so data can be obtained accurately. This is particularly important since EB is a rare condition.

## Conclusion

Based on the results of this study, it can be concluded that the clinical features and laboratory findings of RDEB, as the most commonly found type of EB in our pediatric cohorts, contribute to their nutritional status—in this case, moderate and severe malnutrition. Clinical features of RDEB that contribute to nutritional status include wounds on the skin, tooth decay, hand deformity, and pain when changing dressings. Laboratory findings that contribute to the nutritional status of pediatric EB patients include anemia and low zinc levels. The findings of this study are expected to be useful as baseline data for further studies, including prospective evaluations of nutritional status to the clinical symptoms and nutrition, as well as the quality of life of pediatric EB patients.

## Ethics Approval

This study was conducted in compliance with the Declaration of Helsinki, Good Clinical Practices, and local regulatory requirements, and was approved by the Medical Ethics Committee of Hasan Sadikin General Hospital Bandung (approval number: LB.02.01/X.2.2.1/15095/2020).

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## Disclosure

The authors report no conflicts of interest in this work.

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